

Parental smoking and development of allergic sensitization from birth to adolescence

J. D. Thacher¹, O. Gruziova¹, G. Pershagen^{1,2}, Å. Neuman^{1,3}, M. van Hage⁴, M. Wickman^{1,5}, I. Kull^{1,5,6}, E. Melén^{1,5} & A. Bergström¹

¹Institute of Environmental Medicine, Karolinska Institutet; ²Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm; ³Department of Women's and Children's Health, Uppsala University Hospital, Uppsala; ⁴Clinical Immunology and Allergy Unit, Department of Medicine Solna, Karolinska Institutet and University Hospital; ⁵Sachs' Children's Hospital, Södersjukhuset; ⁶Department of Clinical Science and Education, Karolinska Institutet at Södersjukhuset, Stockholm, Sweden

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Correspondence

Jesse Thacher, MPH, Institute of Environmental Medicine, Karolinska Institutet, Box 210, SE-171 77 Stockholm, Sweden.

Tel.: +46 704 220 115

Fax: +46 830 4571

E-mail: Jesse.Thacher@ki.se

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Abstract

Background: The relation between secondhand tobacco smoke (SHS) exposure and the development of allergic sensitization in children is unclear. The aim of this study was to determine whether maternal smoking during pregnancy and postnatal SHS exposure contributes to the development of allergic sensitization in children and adolescents up to 16 years of age.

Methods: We included 3316 children from a birth cohort followed up for 16 years. SHS exposure and symptoms of allergic disease were assessed using repeated parental questionnaires. Serum immunoglobulin E against eight common inhalant and six food allergens was assessed at ages 4, 8, and 16 years with ImmunoCAP. The association between SHS exposure and sensitization was explored using logistic regression and generalized estimating equations.

Results: Exposure to SHS in infancy without prior exposure *in utero* was associated with an excess risk of food sensitization at age 4 years (OR 1.47, 95% CI 1.08–2.00), with comparable ORs at ages 8 and 16 years. In longitudinal analyses, an overall association was indicated between SHS in infancy and food sensitization up to age 16 years (OR 1.24, 95% CI 0.98–1.56). Maternal smoking during pregnancy was unrelated to sensitization up to 16 years of age. When sensitization was combined with concurrent symptoms of allergic disease, SHS in infancy was associated with an overall elevated risk of eczema with sensitization (OR 1.62, 95% CI 1.20–2.18).

Conclusions: SHS exposure in infancy appears to increase the risk of sensitization to food allergens up to age 16 years, as well as eczema in combination with sensitization.

The prevalence of atopic disease has increased over recent decades, and environmental risk factors and gene-environment interactions play a probable role (1, 2). Despite a declining prevalence of cigarette smoking in many countries, secondhand tobacco smoke (SHS) remains a pervasive indoor environmental risk factor in children of smoking parents. SHS has immunomodulatory effects and is hypothesized to influence the development of allergic sensitization (3). SHS exposure during the fetal period and thereafter has been

associated with both acute and long term adverse health consequences in children and adolescents (4). Mounting evidence links exposure to SHS with respiratory and allergic disease in children, but the impact of tobacco smoke on immunoglobulin E (IgE) mediated sensitization is less clear (5). Some studies report increased risks for any allergen sensitization (1, 6), whereas others report increased risks only for food allergen sensitization (7, 8). Studies have also reported inverse (3, 9, 10) or null associations for inhalant allergens

(4) and there are conflicting data on the role of heredity (1, 3, 6). Possible explanations for the difference in observed results include insufficient control of confounding, the grouping of inhalant and food allergens together, failure to consider possible differing effects of SHS between those with and without family history of atopy, or maternal vs paternal smoking (3). Teasing apart the effects of *in utero* and postnatal SHS exposure remain challenging, but important nonetheless, as the etiological mechanisms may differ depending on timing of exposure.

Few studies have followed children longitudinally from birth to adolescence, and even fewer have collected multiple blood samples. Due to the lack of consistent evidence, we sought to evaluate whether pre- and postnatal SHS exposure contributes to the development of allergic sensitization in a population-based birth cohort study followed longitudinally through adolescence.

Methods

Study subjects

The BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology) study is a longitudinal population-based birth cohort in which infants were recruited at birth and prospectively followed during childhood and adolescence. A total of 4089 infants born in Stockholm, Sweden between 1994 and 1996 were included (11). At a median infant age of 2 months, parents completed the baseline questionnaire which assessed environmental exposures, parental smoking habits, residential characteristics, lifestyle, and parental allergies. When children were approximately ages 1, 2, 4, 8, 12, and 16 years, parents completed questionnaires focusing on symptoms of asthma, rhinitis, and eczema in their children and current parental smoking habits (12). Response rates from baseline were 96%, 94%, 91%, 84%, 82%, and 78%, respectively.

Blood samples were collected at ages 4, 8, and 16 years, and serological allergy IgE testing was performed in 2605 (63.7%), 2470 (60.4%), and 2547 (62.2%) children, respectively.

The baseline and all follow-up studies were approved by the Regional Ethical Review Board, Karolinska Institutet, Stockholm, Sweden, and the parents of all participating children provided informed consent.

Secondhand smoke exposure assessment

Fetal exposure to maternal smoking was defined as daily maternal smoking of one or more cigarettes at any time during pregnancy. Information on maternal smoking during pregnancy was collected at baseline when children were a median age of 2 months. SHS exposure in infancy was defined as maternal and/or paternal smoking of one or more cigarettes per day at baseline. SHS at ages 1, 2, 4, 8, 12, and 16 years of age were defined as maternal and/or paternal smoking of one or more cigarettes daily at the time of the respective follow-up. Information on the average number of cigarettes smoked daily by each parent was collected at each follow-up.

Assessment of allergic sensitization

Allergic sensitization was defined based on IgE antibody reactivity against common inhalant and food allergens. At each follow-up, sera were screened with Phadiatop[®], a mix of typical inhalant allergens: pollens of birch, timothy, and mugwort, danders of cat, dog and horse, mold [*Cladosporium herbarum*], and house dust mite [*Dermatophagoides pteronyssinus*], and fx5[®], a mix of typical food allergens: cow's milk, hen's egg, soy bean, peanut, cod fish and wheat (ImmunoCAP System; Thermo Fisher/Phadia AB, Uppsala, Sweden). Sera that scored positive for Phadiatop[®] or fx5[®] were subsequently analyzed for allergen-specific IgE antibodies to the single inhalant and food allergens mentioned above. Any allergen sensitization was defined as a positive reaction, 0.35 kU_A/l or more, to any of the allergens tested. Inhalant allergens were classified as either indoor (cat, dog, horse, and/or house dust mite) or outdoor (timothy grass, birch, mugwort, and/or mold). The reference groups were made up of subjects not sensitized against the allergens being tested.

Assessment of asthma, rhinitis and eczema

The assessment of asthma, rhinitis and eczema were based on parental questionnaires at ages 4, 8, and 16 years.

Asthma: four or more episodes of wheeze in the last 12 months or one or more episode of wheeze in the last 12 months in combination with inhaled steroids (12).

Rhinitis: eye or nose symptoms following exposure to allergens in the last 12 months and/or a doctor's diagnosis of allergic rhinitis (12).

Eczema: dry skin, pruritic rash with age-specific localizations at face, flexures of arms or legs, wrists or ankles, or neck in the last 12 months and/or a doctor's diagnosis of eczema (12).

Statistical analyses

Chi-square tests were used to test for differences in covariates between groups of children exposed to maternal smoking during pregnancy (*in utero*) and in infancy. Associations between SHS exposure and allergic sensitization were analyzed with SHS allocated into four categories: (i) no exposure *in utero* or in infancy (reference category), (ii) only *in utero*, (iii) only in infancy, and (iv) both during *in utero* and in infancy. The association between these categories and sensitization were analyzed using multinomial logistic regression. All associations are reported as odds ratios (ORs) and 95% confidence intervals (CIs), and $P < 0.05$ was considered statistically significant. Associations between SHS and allergic sensitization were also analyzed longitudinally using generalized estimating equation (GEE) models with an unstructured correlation matrix (13). This model included an interaction term between the time indicator variable and exposure to evaluate the effect of exposure over time (13). In these analyses, exposure to maternal smoking during pregnancy and parental smoking in infancy were dichotomized (yes vs no) to increase power and robustness. To examine dose-response

associations between the numbers of cigarettes smoked per day and sensitization, we defined three categories for exposure to maternal smoking during pregnancy: (i) no cigarettes throughout pregnancy (reference category), (ii) 1–9 cigarettes per day during any trimester, and (iii) ≥ 10 cigarettes per day during any trimester. Similar categories were coded for parental smoking in infancy, for each parent individually and then combined: (i) mother and father did not smoke (reference category), (ii) mother/father smoked 1–9 cigarettes per day, and (iii) mother/father smoked ≥ 10 cigarettes per day.

To account for the effect of smoking throughout early childhood and adolescence a 'smoking throughout childhood' variable was constructed. This was defined based on the responses (yes vs no) in the questionnaires prior to the blood sample collection at 4, 8, and 16 years. For example, parental smoking assessed at ages 1 and 2 were combined and regressed against outcomes assessed at year 4.

To elucidate the effect of SHS on sensitization combined with symptoms of asthma, rhinitis and eczema, categorical variables were created. Asthma was categorized into: (i) no asthma and no sensitization (reference category), (ii) asthma without any sensitization, (iii) asthma with any sensitization, and (iv) any sensitization only. Similar categories were created for rhinitis and eczema. Corresponding categories were also used in analyses focused on food allergen sensitization and symptoms of asthma, rhinitis, and eczema.

Various covariates were tested through exploratory stepwise logistic regression to identify potential confounding factors. Models tested included sex, duration of breastfeeding, socioeconomic status (categorized on the basis of parents' occupation as manual and nonmanual workers), construction year of home, presence of siblings, maternal age, reported dampness or mold in the home at birth, air pollution from local road traffic (14) (using NO_x as indicator), parental allergic disease, cat or dog ownership, birth weight and children's own smoking history. Covariates leading to $> 5\%$ change in estimates were kept in the final models and included parental allergy and socioeconomic status. To disentangle the effects of maternal smoking during pregnancy and parental smoking in infancy from that of exposure to SHS at ages 1–16 years, we created models adjusted for SHS throughout childhood (ages 1–16 years).

Because GEE models can provide an estimate when observations are missing or unequally spaced, we included all children who gave at least one blood sample in the final analyses (13). A total of 3316 children with complete information on exposure, confounders, and blood samples were included in the final analyses.

All statistical analyses were performed with STATA (release 12; Stata Corp., College Station, TX, USA).

Results

The 3316 children included in this study were comparable to the original cohort regarding distribution of background characteristics such as SHS exposure (Table S1). In total, 12.6% were exposed to maternal smoking during pregnancy and 20.8% to SHS by any parent in infancy. A substantial

proportion of mothers who smoked in infancy had also smoked during pregnancy (Figure S1). Maternal smoking during pregnancy, low parental socioeconomic status, low maternal age, and furred pets at home were more prevalent among children exposed to parental smoking in infancy (Table S2). Parental allergy and longer duration of breastfeeding were less frequent among children exposed to SHS in infancy. Similar patterns were observed in children exposed to maternal smoking during pregnancy (data not shown). Parental smoking was highest in infancy and declined to 13.5% at the 16 year follow-up.

Prevalence rates of sensitization to any inhalant or food allergen at ages 4, 8, and 16 were 24.1%, 34.8%, and 45.9%, respectively (Table S3). There was considerable overlap between any sensitization at ages 4, 8, and 16 years, indicating that few children lost their sensitization (Fig. 1) (15). The prevalence of asthma, rhinitis, and eczema at age 16 years were 6%, 26%, and 9%, respectively.

To try to disentangle the influence of pre- and postnatal SHS exposure, maternal smoking during pregnancy and parental smoking in infancy were allocated into four categories. Among children exposed to maternal smoking during pregnancy but not SHS in infancy, we observed no association with sensitization to any (inhalant or food) allergen at ages 4, 8, and 16 years (Table 1). However, children exposed in infancy without prior exposure to maternal smoking during pregnancy, had an increased risk of food sensitization at age 4 years (OR 1.47, 95% CI 1.08–2.00), and a tendency for increased risks which were no longer statistically significant at 8 (OR 1.34, 95% CI 0.99–1.79) and 16 years (OR 1.32, 95% CI 0.93–1.86). Moreover, these children had significantly increased odds of persistent food allergen sensitization up to age 16 years (OR 2.17, 95% CI 1.32–3.56) (Table S4). In addition, there was an increased risk of sensitization to indoor allergens at age 4 years for these children (OR 1.50, 95% CI 1.00–2.24). We observed no significantly increased

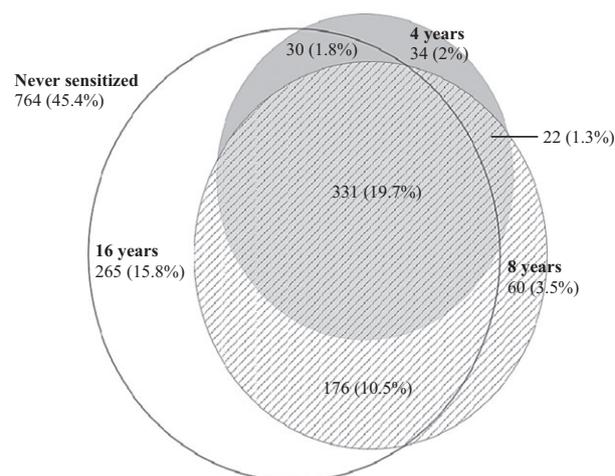


Figure 1 Prevalence and proportional relationship of any sensitization at 4, 8, and 16 years among children in the BAMSE birth cohort ($n = 1682$).

Table 1 Associations between maternal smoking during pregnancy (*in utero*) and parental smoking in infancy (SHS) in relation to sensitization at 4, 8, and 16 years of age among children in the BAMSE birth cohort (*n* = 3316)**

	N	Any allergen*¶		Indoor allergens†¶		Outdoor allergens‡¶		Food allergens§¶	
		<i>n</i>	OR (95% CI)	<i>n</i>	OR (95% CI)	<i>n</i>	OR (95% CI)	<i>n</i>	OR (95% CI)
4 Years									
No exposure <i>in utero</i> or SHS	1962	457	Referent	155	Referent	216	Referent	289	Referent
Exposure <i>in utero</i> but not to SHS	102	25	0.98 (0.61–1.58)	10	1.11 (0.54–2.25)	11	0.84 (0.43–1.64)	18	1.20 (0.71–2.03)
Exposure to SHS but not <i>in utero</i>	309	81	1.16 (0.88–1.54)	34	1.50 (1.00–2.24)	35	1.08 (0.74–1.59)	64	1.47 (1.08–2.00)
Exposure to <i>in utero</i> and SHS	219	61	1.16 (0.84–1.62)	25	1.41 (0.87–2.28)	30	1.14 (0.73–1.77)	40	1.17 (0.80–1.72)
8 Years									
No exposure <i>in utero</i> or SHS	1845	642	Referent	328	Referent	397	Referent	353	Referent
Exposure <i>in utero</i> but not to SHS	91	33	1.03 (0.66–1.62)	19	1.14 (0.66–1.95)	22	1.07 (0.64–1.78)	19	1.12 (0.67–1.89)
Exposure to SHS but not <i>in utero</i>	305	104	0.97 (0.74–1.26)	51	0.93 (0.67–1.31)	58	0.88 (0.64–1.21)	75	1.34 (0.99–1.79)
Exposure to <i>in utero</i> and SHS	193	66	0.99 (0.72–1.38)	29	0.84 (0.55–1.29)	36	0.83 (0.56–1.23)	41	1.13 (0.78–1.65)
16 Years									
No exposure <i>in utero</i> or SHS	1937	891	Referent	586	Referent	662	Referent	242	Referent
Exposure <i>in utero</i> but not to SHS	89	40	0.94 (0.60–1.46)	22	0.73 (0.44–1.22)	30	0.95 (0.60–1.52)	11	0.90 (0.46–1.77)
Exposure to SHS but not <i>in utero</i>	310	144	1.04 (0.81–1.33)	93	1.03 (0.79–1.35)	99	0.94 (0.72–1.22)	50	1.32 (0.93–1.86)
Exposure to <i>in utero</i> and SHS	195	88	0.99 (0.73–1.35)	54	0.90 (0.63–1.27)	49	0.68 (0.47–0.96)	28	1.19 (0.77–1.86)

*Any positive inhalant and/or any food allergen.

†Sensitization to cat, dog, horse, or mite.

‡Sensitization to timothy, birch, mugwort, or mold.

§Sensitization to cow's milk, hen's egg, soy bean, peanut, cod fish, or wheat.

¶Adjusted for heredity and socioeconomic status.

**Odds ratio (OR) and 95% confidence intervals (CI) obtained from multinomial logistic regression.

risk of any sensitization when children were exposed to both maternal smoking during pregnancy and infancy SHS. However, there was an indication of an inverse association between allergic sensitization to outdoor allergens in children exposed to both maternal smoking during pregnancy and SHS in infancy, with a statistically significant reduced risk of outdoor allergen sensitization at 16 years of age (OR 0.68, 95% CI 0.47–0.96).

When assessing the longitudinal effects of SHS exposure, maternal smoking during pregnancy and parental smoking in infancy were analyzed separately to increase power and robustness. There were no overall increased risks of any, indoor, outdoor, or food allergen sensitization up to age 16 years among children exposed to maternal smoking during pregnancy (data not shown). In contrast, there was a suggestion of an overall increased risk of food sensitization up to age 16 years among children exposed to parental smoking in infancy (OR 1.24, 95% CI 0.98–1.56) (Fig. 2). Age-specific associations were suggested for food allergen sensitization at all ages. These associations persisted after further adjustment for maternal smoking during pregnancy, although failing to reach statistical significance (OR 1.25, 95% CI 0.98–1.60 for the overall association). Furthermore, we observed an increased risk of any inhalant or food allergen as well as indoor inhalant allergen sensitization at age 4 years, but not at older ages or overall (Fig. 2).

Stratified analyses showed no significant differences in SHS in infancy and food sensitization among those with and without parental allergic disease (OR 1.36, 95% CI 0.90–2.06 and OR 1.17, 95% CI 0.88–1.57, respectively) (Table S5). Moreover, we found no statistically significant interaction between SHS in infancy and parental allergic disease ($P = 0.94$). Likewise, these analyses were stratified by maternal smoking during pregnancy, and we observed excess risk in children only exposed in infancy (OR 1.33, 95% CI 1.01–1.75) compared to those exposed both in infancy and to maternal smoking during pregnancy (OR 0.97, 95% CI 0.57–1.64) (Table S5).

No evidence of interaction was observed between maternal smoking during pregnancy and SHS in infancy ($P = 0.30$).

In analyses of single allergens, SHS exposure in infancy was associated with a statistically significant increased risk of sensitization to cow's milk (OR 1.32, 95% CI 1.02–1.70), and positive associations were also suggested for all other food allergens with the exception of cod fish (Table 2). An increased risk of mold sensitization in relation to infancy SHS exposure was also observed (OR 1.81, 95% CI 1.10–2.99).

When we explored the dose–response association between SHS exposure in infancy and the development of sensitization, we observed increased risks of any (OR 1.36, 95% CI 1.06–1.74), indoor (OR 1.42, 95% CI 1.05–1.91), and food allergen (OR 1.61, 95% CI 1.20–2.16) sensitization among children whose fathers smoked ≥ 10 cigarettes per day in infancy (Table 3). A significant trend of greater number of cigarettes was observed for any and food sensitization, P_{trend} 0.04 and 0.003, respectively. Comparable associations were observed among children exposed to ≥ 10 cigarettes per day by both parents with any (OR 1.71, 95% CI 1.00–2.95) and food (OR 1.70, 95% CI 0.90–3.22) allergen sensitization.

Associations between SHS exposure in infancy in relation to asthma, rhinitis, and eczema in combination with sensitization to any common allergens are presented in Fig. 3, A. No significant associations were seen for asthma with or without sensitization. In contrast, a positive association was observed for rhinitis, but only among nonsensitized children (OR 1.53, 95% CI 1.01–2.31). We also observed elevated overall (OR 1.62, 95% CI 1.20–2.18) and age-specific excess risks of eczema with any sensitization in relation to SHS exposure in infancy. The same analyses were performed among those children sensitized against food allergens (Fig. 3, B), providing similar results.

In sensitivity analyses further adjustment for the children's own smoking at age 16 years had no major influence on the observed odds ratios between infancy SHS exposure and

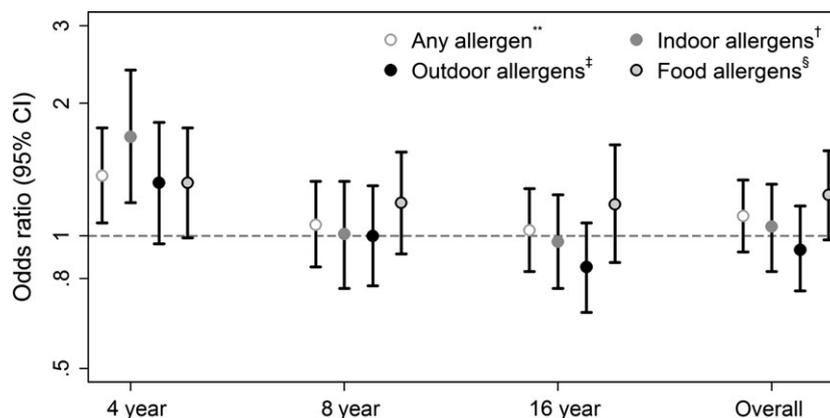


Figure 2 Association between exposure to SHS during infancy and the risk of allergic sensitization during the first 16 years of life among children in the BAMSE birth cohort ($n = 3316$). **Any inhalant and/or any food allergen positive. †Sensitization to cat, dog,

horse, or mite. ‡Sensitization to timothy, birch, mugwort, or mold. §Sensitization to cow's milk, hen's egg, soy bean, peanut, cod fish, or wheat. Adjusted for heredity, socioeconomic status, and smoking after infancy.

Table 2 Associations between parental smoking in infancy (SHS) and the risk of sensitization to individual allergens up to 16 years of age among children in the BAMSE birth cohort ($n = 3316$)‡

Allergen*	Parental smoking in infancy	
	OR (95% CI)†	P-value
Birch		
No SHS	Referent	
Yes SHS	0.93 (0.74–1.16)	0.52
Timothy		
No SHS	Referent	
Yes SHS	0.81 (0.65–1.01)	0.06
Mugwort		
No SHS	Referent	
Yes SHS	0.71 (0.51–0.97)	0.03
Cat		
No SHS	Referent	
Yes SHS	1.12 (0.88–1.42)	0.35
Dog		
No SHS	Referent	
Yes SHS	0.98 (0.77–1.23)	0.84
Horse		
No SHS	Referent	
Yes SHS	1.31 (0.98–1.76)	0.07
Dust Mite		
No SHS	Referent	
Yes SHS	0.92 (0.68–1.23)	0.56
Mold		
No SHS	Referent	
Yes SHS	1.81 (1.10–2.99)	0.02
Cow's Milk		
No SHS	Referent	
Yes SHS	1.32 (1.02–1.70)	0.03
Peanut		
No SHS	Referent	
Yes SHS	1.26 (0.93–1.71)	0.14
Hen's Egg		
No SHS	Referent	
Yes SHS	1.20 (0.86–1.67)	0.29
Wheat		
No SHS	Referent	
Yes SHS	1.20 (0.87–1.67)	0.27
Soy bean		
No SHS	Referent	
Yes SHS	1.20 (0.83–1.73)	0.33
Fish		
No SHS	Referent	
Yes SHS	1.01 (0.38–2.68)	0.98

*Sensitization defined as IgE \geq 0.35 kU_A/l.

†Adjusted for heredity and socioeconomic status.

‡Analyses done with generalized estimating equations GEE).

food sensitization (OR 1.28, 95% CI 1.00–1.64). Analyses were also performed with a higher antibody cut off of 3.5 kU_A/l, and this did not significantly alter our findings (data not shown). Furthermore, analyses were conducted for inhalant, food, and single allergens using a reference group comprised of subjects without sensitization to any allergen, but showed no considerable differences.

Discussion

In this population-based birth cohort followed up for 16 years, children exposed to parental smoking in infancy without prior exposure *in utero* had an increased risk for food allergen sensitization at age 4 years, with comparable associations at ages 8 and 16 years. Additionally, increased risk of indoor allergen sensitization at 4 years was observed among these children, but was no longer apparent at ages 8 or 16 years. A tendency of an overall association between SHS exposure in infancy and allergic sensitization to food allergens up to adolescence was suggested in longitudinal analyses. Moreover, there was a dose-dependent association with an increasing number of cigarettes smoked by fathers in infancy. In contrast, there were no clear associations between maternal smoking during pregnancy and sensitization to inhalant or food allergens in the offspring. When we combined symptoms of allergic disease with sensitization status, we found that exposure to SHS in infancy was associated with excess risk of eczema with sensitization, but not eczema without sensitization.

Our finding that exposure to SHS in infancy is associated with an increased risk of sensitization to food allergens is in agreement with earlier studies in children between the ages of three and 4 years (7, 8). To our knowledge, our study is the first to indicate that the increased risk of food sensitization persists into adolescence. The German birth cohort, Multi-center Allergy Study (MAS), followed up to 10 years of age reported an increased risk of any sensitization among children exposed to regular maternal smoking, but only in children with a genetic predisposition (1). We observed similar risks of food sensitization irrespective of parental history of allergy.

A recent systematic review and meta-analysis reported that exposure to postnatal parental smoking was associated with significantly higher total IgE concentrations, IgE antibodies to common allergens, and positive skin prick tests in pre-school and school age children (16). However, the authors were unable to disentangle food sensitization from inhalant allergen sensitization. A study from the MAS birth cohort did differentiate between specific types of allergens as well as the effects of pre- vs postnatal parental smoking (8). They reported that preschool age children unexposed during pregnancy but exposed in early life had comparatively increased risks of food allergen sensitization as those children exposed both pre- and postnatally (8). In contrast, an earlier systematic review, as well as a UK birth cohort, found no associations between SHS exposure before or after birth and sensitization (17, 18). A lack of association between maternal smoking during pregnancy and sensitization in children at age 14 years was also shown in a recent report from an Australian birth cohort (19). In the present study, we observed no association with maternal smoking during pregnancy. In addition, we observed an attenuation of the risk in children exposed to both maternal smoking during pregnancy and parental SHS in infancy. One possible explanation for this is that exposure during pregnancy could preclude sensitization through an immunosuppressive effect (20–22), whereas

Table 3 Associations between maternal smoking during pregnancy and parental smoking in infancy in relation to smoking intensity and overall risk of sensitization up to 16 years of age among children in the BAMSE birth cohort ($n = 3316$)*

	Maternal smoking during pregnancy		Parental smoking in infancy		
	Mother† OR (95% CI)		Mother‡ OR (95% CI)	Father‡ OR (95% CI)	Both Parents‡ OR (95% CI)
Any allergen§					
No smoking	Referent		Referent	Referent	Referent
Total of 1–9 cigarettes/day	1.04 (0.76–1.42)		1.43 (0.98–2.06)	0.87 (0.65–1.16)	0.96 (0.42–2.18)
Total of ≥10 cigarettes/day	1.02 (0.76–1.36)		1.21 (0.82–1.75)	1.36 (1.06–1.74)	1.71 (1.00–2.95)
P_{trend}	0.86		0.15	0.04	0.07
Indoor allergens¶					
No smoking	Referent		Referent	Referent	Referent
Total of 1–9 cigarettes/day	0.76 (0.51–1.16)		1.18 (0.74–1.87)	0.69 (0.47–1.01)	0.58 (0.17–1.96)
Total of ≥10 cigarettes/day	1.09 (0.76–1.55)		1.13 (0.71–1.80)	1.42 (1.05–1.91)	1.30 (0.67–2.53)
P_{trend}	0.96		0.49	0.10	0.63
Outdoor allergens**					
No smoking	Referent		Referent	Referent	Referent
Total of 1–9 cigarettes/day	0.88 (0.60–1.29)		1.13 (0.73–1.77)	0.77 (0.54–1.09)	0.96 (0.36–2.59)
Total of ≥10 cigarettes/day	1.00 (0.71–1.42)		0.99 (0.63–1.56)	1.04 (0.77–1.39)	1.24 (0.65–2.38)
P_{trend}	0.86		0.87	0.87	0.55
Food allergens††					
No smoking	Referent		Referent	Referent	Referent
Total of 1–9 cigarettes/day	0.90 (0.61–1.33)		1.09 (0.68–1.74)	1.01 (0.71–1.45)	0.64 (0.19–2.17)
Total of ≥10 cigarettes/day	0.93 (0.66–1.33)		1.16 (0.73–1.84)	1.61 (1.20–2.16)	1.70 (0.90–3.22)
P_{trend}	0.63		0.50	0.003	0.18

*Odds ratio (OR) and 95% confidence intervals (CI) obtained from generalized estimating equations (GEE).

†Adjusted for socioeconomic status, heredity, and postnatal smoking.

‡Adjusted for socioeconomic status, heredity, and smoking after infancy.

§Any inhalant and/or any food allergen positive.

¶Sensitization to cat, dog, horse, or mite.

**Sensitization to timothy, birch, mugwort, or mold.

††Sensitization to cow's milk, hen's egg, soy bean, peanut, cod fish, or wheat.

exposure following birth confers risk of allergic sensitization (5). This could partly explain the divided literature on SHS exposure and sensitization, as some studies did not differentiate between pre- and postnatal SHS exposure.

We also observed an increased risk of mold sensitization in relation to infancy SHS exposure; however this finding should be interpreted with caution, as there were only 48 children sensitized against mold at age 16 years.

The presence of a dose–response association between SHS in infancy in our study and sensitization further reinforces our findings. Although the dose–response association was mainly observed in fathers, this may be because fathers were more likely than mothers to smoke and did so more heavily. Moreover, we observed larger risks of sensitization when both heavy smoking mothers and fathers were combined.

Although sensitization and allergic disease are interrelated, it is important to keep in mind that sensitization is not synonymous with allergic disease. Instead, the combination of symptoms and serologic measures of allergen-specific IgE antibodies provided us with a more accurate picture of how SHS exposure affects allergic disease. In our study, we observed comparable associations between SHS exposure in

infancy and asthma with and without concurrent sensitization. In contrast, an earlier study indicated a stronger association for asthma without sensitization (23). Focusing on any sensitization, SHS exposure in infancy was associated with an increased risk of rhinitis without sensitization in our study. Consistent with earlier studies in preschool age children, our study showed that SHS exposure in infancy increased the risk of eczema in combination with sensitization (24, 25).

The potential mechanisms behind the increased risk for sensitization in children of smoking parents are not fully understood. The 'mucosal concept of atopy' proposes that sensitization occurs mainly in the mucosal surfaces of the airways and that mucosal insults and inflammation facilitate antigen penetration and thus subsequent sensitization (26). Although it may seem puzzling that SHS should increase the risk of sensitization to food allergens, food allergens are frequently found in dust and are likely to be inhaled by infants. Infants often inhale or aspirate while eating and expose both the pharynx and pharyngeal lymphoid tissues to food allergens (as well as to tobacco smoke) (7). Furthermore, nicotine is known to have immunomodulatory effects and could thereby influence sensitization, although the exact mech-

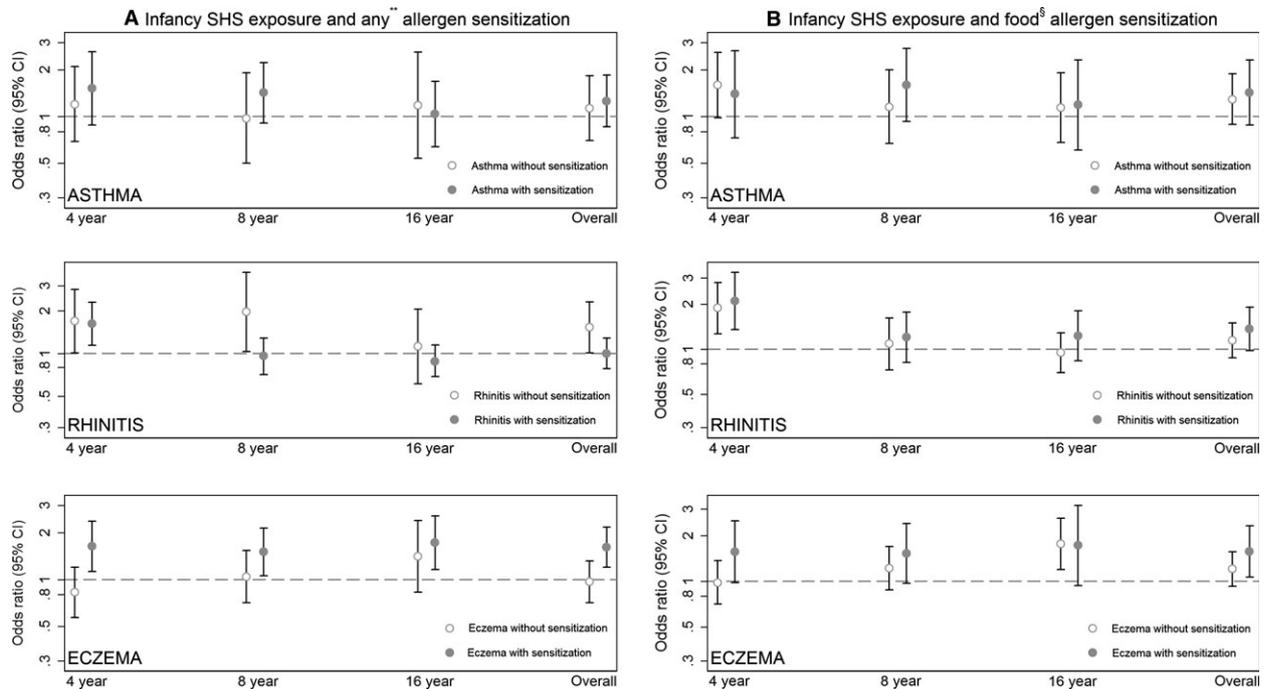


Figure 3 Association between parental smoking during infancy and the risk of any or food sensitization and allergic disease among children in the BAMSE birth cohort ($n = 3316$). **Any inhalant and/

or any food allergen positive. [§]Sensitization to cow's milk, hen's egg, soy bean, peanut, cod fish, or wheat. Adjusted for heredity, socioeconomic status, and smoking after infancy.

anism is unknown (22). Alternatively, the dual-allergen-exposure hypothesis suggests that exposure through the skin leads to sensitization, whereas consumption of allergens leads to oral tolerance (27). As tobacco smoke has been shown to negatively affect skin barrier function and the ingress of allergens, food allergen sensitization is possibly influenced by the effect of SHS exposure on the skin (28, 29). Akin to our findings, studies exploring the risks of ambient traffic-related air pollution – which may act through the same biological mechanisms as SHS – describe an increased risk of sensitization against food allergens associated with exposure in infancy (14, 30).

Several strengths of this study include its prospective and population-based design, large size, high response rates, the use of validated questions based on the International Study of Asthma and Allergies in Childhood (ISAAC) (31), and questions used in other birth cohort studies (32). The collection of blood samples at three time points coupled with repeated questionnaires assessing SHS exposure enabled us to perform longitudinal analyses. Moreover, using Phadiatop[®] and fx5[®] we were able to detect greater than 90% of all sensitization in our study population. Information on maternal smoking during pregnancy and parental smoking in infancy were collected shortly after birth, thus reducing the likelihood of recall bias regarding smoking habits. Due to the large number of blood samples collected, we were able to differentiate between sensitization of specific inhalant and food allergens. The overall prevalence of sensitization

increased with age and recent work from this same cohort indicates that the increase in sensitization is a dynamic process (33).

Limitations such as misclassification of exposure are often present in observational studies and should be acknowledged. SHS exposure was determined using questionnaires, so misclassification to some degree cannot be excluded. The prevalence of smoking may be underestimated due to the social stigmatization surrounding smoking, particularly in the context of children and health (34), and would lead to an attenuation of the true effect comparing dichotomous exposure categories. However, it is important to keep in mind that exposure information was assessed shortly following birth, thus parental responses would not be biased based on children's health or symptoms. Another potential limitation is the lack of information on paternal smoking during pregnancy assessed at baseline. Maternal passive smoking has been shown to increase the risk of allergic disease in children (35, 36), and could have an effect on IgE sensitization. Nevertheless, we saw no indication of an association between maternal smoking during pregnancy and sensitization, so it is unlikely that maternal passive smoking during pregnancy would significantly alter our findings.

In conclusion, our findings suggest that exposure to parental smoking in early infancy increases the risk of sensitization to food allergens up to 16 years. Exposure to SHS in infancy

was also associated with an excess risk of eczema with sensitization. Exposure to maternal smoking during pregnancy was unrelated to sensitization up to 16 years of age.

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Conflict of interest

The authors have no potential conflicts of interest to disclose.

Author contributions

MW and GP initiated the BAMSE cohort. JDT, OG, GP, ÅN, MvH, MW, IK, EM, and AB participated in the design and planning of the current study. JDT performed the data

analyses and drafted the initial manuscript. MvH supervised the analysis of blood samples. All authors participated in the interpretation of the findings, provided critical review, and approved the final manuscript as submitted.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Prevalence and proportional relationship of maternal smoking during pregnancy and parental smoking in infancy ($n = 3290$).

Figure S2. Distribution of food sensitization at 4, 8, and 16 years of age ($n = 1684$).

Table S1. Distribution of selected exposure characteristics among all children in the BAMSE cohort ($n = 4089$) and children who gave blood at ages 4, 8 and 16 years and those children included in the current analyses ($n = 3316$).

Table S2. Distribution of selected exposure characteristics in relation to parental smoking during infancy among children in the BAMSE birth cohort ($n = 3316$).

Table S3. Prevalence of sensitization at 4, 8, and 16 years of age among children in the BAMSE birth cohort ($n = 3316$).

Table S4. Associations between maternal smoking during pregnancy (*in utero*) and parental smoking in infancy (SHS) in relation to transient* and persistent† food allergen sensitization at 4, 8, and 16 years of age among children in the BAMSE birth cohort ($n = 3316$)*.*.

Table S5. Risk of food sensitization up to 16 years in relation to parental smoking in infancy stratified by parental allergic disease and maternal smoking during pregnancy among children in the BAMSE birth cohort ($n = 3316$)*.

References

- Keil T, Lau S, Roll S, Gruber C, Nickel R, Niggemann B et al. Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. *Allergy* 2009;**64**:445–451.
- Kabesch M. Gene by environment interactions and the development of asthma and allergy. *Toxicol Lett* 2006;**162**:43–48.
- Hancox RJ, Welch D, Poulton R, Taylor DR, McLachlan CR, Greene JM et al. Cigarette smoking and allergic sensitization: a 32-year population-based cohort study. *J Allergy Clin Immunol* 2008;**121**:38–42.
- Ciaccio CE, DiDonna AC, Kennedy K, Barnes CS, Portnoy JM, Rosenwasser LJ. Association of tobacco smoke exposure and atopic sensitization. *Ann Allergy Asthma Immunol* 2013;**111**:387–390.
- Ciaccio CE, Gentile D. Effects of tobacco smoke exposure in childhood on atopic diseases. *Curr Allergy Asthma Rep* 2013;**13**:687–692.
- Havstad SL, Johnson CC, Zoratti EM, Ezell JM, Woodcroft K, Ownby DR et al. Tobacco smoke exposure and allergic sensitization in children: a propensity score analysis. *Respirology* 2012;**17**:1068–1072.
- Lannerö E, Wickman M, van Hage M, Bergström A, Pershagen G, Nordvall L. Exposure to environmental tobacco smoke and sensitisation in children. *Thorax* 2008;**63**:172–176.
- Kulig M, Luck W, Lau S, Niggemann B, Bergmann R, Klette U et al. Effect of pre- and postnatal tobacco smoke exposure on specific sensitization to food and inhalant allergens during the first 3 years of life. Multicenter Allergy Study Group, Germany. *Allergy* 1999;**54**:220–228.
- Vonk JM, Boezen HM, Postma DS, Schouten JP, van Aalderen WM, Boersma ER. Perinatal risk factors for bronchial hyperresponsiveness and atopy after a follow-up of 20 years. *J Allergy Clin Immunol* 2004;**114**:270–276.
- Kuyucu S, Saraclar Y, Tuncer A, Sackesen C, Adalioglu G, Sumbuloglu V et al. Determinants of atopic sensitization in Turkish school children: effects of pre- and post-natal events and maternal atopy. *Pediatr Allergy Immunol* 2004;**15**:62–71.
- Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol* 2002;**13**(Suppl 15):11–13.
- Thacher JD, Gruzjeva O, Pershagen G, Neuman A, Wickman M, Kull I et al. Pre- and Postnatal Exposure to Parental Smoking and Allergic Disease Through Adolescence. *Pediatrics* 2014;**134**:428–434.
- Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis*. 2nd ed. Hoboken, NJ: Wiley; 2011.
- Gruzjeva O, Bellander T, Eneroth K, Kull I, Melen E, Nordling E et al. Traffic-related air pollution and development of allergic

- sensitization in children during the first 8 years of life. *J Allergy Clin Immunol* 2012;**129**:240–246.
15. Rodgers P, Stapleton G, Flower J, Howse J. Drawing area-proportional Euler diagrams representing up to three sets. *IEEE Trans Vis Comput Graph* 2014;**20**:56–69.
 16. Feleszko W, Ruszczynski M, Jaworska J, Strzelak A, Zalewski BM, Kulus M. Environmental tobacco smoke exposure and risk of allergic sensitisation in children: a systematic review and meta-analysis. *Arch Dis Child* 2014;**99**:985–992.
 17. Strachan DP, Cook DG. Health effects of passive smoking.5. Parental smoking and allergic sensitisation in children. *Thorax* 1998;**53**:117–123.
 18. Murray CS, Woodcock A, Smillie FI, Cain G, Kissen P, Custovic A et al. Tobacco smoke exposure, wheeze, and atopy. *Pediatr Pulmonol* 2004;**37**:492–498.
 19. Hollams EM, de Klerk NH, Holt PG, Sly PD. Persistent effects of maternal smoking during pregnancy on lung function and asthma in adolescents. *Am J Respir Crit Care Med* 2014;**189**:401–407.
 20. Salo PM, Arbes SJ Jr, Jaramillo R, Calatroni A, Weir CH, Sever ML et al. Prevalence of allergic sensitization in the United States: Results from the National Health and Nutrition Examination Survey (NHANES) 2005–2006. *J Allergy Clin Immunol* 2014;**134**:350–359.
 21. Accordini S, Janson C, Svanes C, Jarvis D. The role of smoking in allergy and asthma: lessons from the ECRHS. *Curr Allergy Asthma Rep* 2012;**12**:185–191.
 22. Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol* 2002;**2**:372–377.
 23. Ronmark E, Jonsson E, Platts-Mills T, Lundback B. Different pattern of risk factors for atopic and nonatopic asthma among children—report from the Obstructive Lung Disease in Northern Sweden Study. *Allergy* 1999;**54**:926–935.
 24. Krämer U, Lemmen CH, Behrendt H, Link E, Schäfer T, Gostomzyk J et al. The effect of environmental tobacco smoke on eczema and allergic sensitization in children. *Br J Dermatol* 2004;**150**:111–118.
 25. Bohme M, Kull I, Bergstrom A, Wickman M, Nordvall L, Pershagen G et al. Parental smoking increases the risk for eczema with sensitization in 4-year-old children. *J Allergy Clin Immunol* 2010;**125**:941–943.
 26. Leskowitz S, Salvaggio JE, Schwartz HJ. An hypothesis for the development of atopic allergy in man. *Clin Allergy* 1972;**2**:237–246.
 27. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008;**121**:1331–1336.
 28. Muizzuddin N, Marenus K, Vallon P, Maes D. Effect of cigarette smoke on skin. *J Soc Cosmet Chem* 1997;**48**:235–242.
 29. Biagini Myers JM, Khurana Hershey GK. Eczema in early life: genetics, the skin barrier, and lessons learned from birth cohort studies. *J Pediatr* 2010;**157**:704–714.
 30. Brauer M, Hoek G, Smit HA, de Jongste JC, Gerritsen J, Postma DS et al. Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur Respir J* 2007;**29**:879–888.
 31. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483–491.
 32. Bousquet J, Burney PG, Zuberbier T, Cauwenberge PV, Akdis CA, Bindslev-Jensen C et al. GA2LEN (Global Allergy and Asthma European Network) addresses the allergy and asthma 'epidemic'. *Allergy* 2009;**64**:969–977.
 33. Wickman M, Asaranoj A, Tillander H, Andersson N, Bergstrom A, Kull I et al. Childhood-to-adolescence evolution of IgE antibodies to pollens and plant foods in the BAMSE cohort. *J Allergy Clin Immunol* 2013;**133**:580–582.
 34. Stuber J, Galea S, Link BG. Smoking and the emergence of a stigmatized social status. *Soc Sci Med* 2008;**67**:420–430.
 35. Lee SL, Lam TH, Leung TH, Wong WH, Schooling M, Leung GM et al. Foetal exposure to maternal passive smoking is associated with childhood asthma, allergic rhinitis, and eczema. *ScientificWorldJournal* 2012;**2012**:542983.
 36. Xepapadaki P, Manios Y, Liarigkiovinos T, Grammatikaki E, Douladiris N, Kort-salioudaki C et al. Association of passive exposure of pregnant women to environmental tobacco smoke with asthma symptoms in children. *Pediatr Allergy Immunol* 2009;**20**:423–429.